REMARKS/ARGUMENTS

Reconsideration of this patent application is respectfully requested in view of the foregoing amendments, and the following remarks.

The claims are 1, 2 and 4-24. Independent claims 1, 2, 13, 14 and 24 have been amended to more clearly define the invention. In particular, claims 1, 2 and 24 have been amended to recite a device comprising an "*evaluation unit that detects the proportion of the emitted near infrared radiation that exits from tissue of the organ as a single input signal*". Likewise, method claims 13 and 14 have been amended to recite the step of "*detecting a proportion of the emitted near infrared radiation that exits from the organ at a second location as a single input signal*".

Claims 1, 2 and 24 have also been amended to delete the recitation of the input signal comprising a pulsatile component and a non-pulsatile component and to recite that the evaluation unit is programmed to, *inter alia*, divide up "*said single input signal into a pulsatile component and a non-pulsatile component*". Method claims 13 and 14 have also been amended to delete the

recitation of the input signal having a pulsatile component and a non-pulsatile component and to recite the step of "*dividing up said single input signal into a pulsatile component and a non-pulsatile component*".

Support for the amendments to claims 1, 2, 13, 14 and 24 may be found, *inter alia*, in the claims as filed, in the written description as filed at pages 5-6, and 11 and in FIG. 2 as filed. No new matter has been introduced.

Claims 1, 4, 7-9, 11, 12, 13, 16, 20, 22 and 23 were rejected under 35 U.S.C. 103(a) as being unpatentable over *U.S. Patent No. 6,223,069 to Pfeiffer et al.*, in view of U.S. Patent No. 6,709,402 to *Dekker*. Claims 2, 5, 6, 10, 14, 15, 17, 18, 21 and 24 were rejected under 35 U.S.C. 103(a) as being unpatentable over *Pfeiffer et al* in view of *Dekker* and further in view of *U.S. Patent No. 6,516,214 to Boas*.

Essentially the Examiner's position was that *Pfeiffer et al.* discloses the device for measuring cerebral blood flow in an organ using an injected indicator substantially as recited in claims 1, 4, 7-9, 11, 12, 13, 16, 20, 22 and 23 with the

exception of using the non-pulsatile signal component in determination of concentration and blood flow. In the Examiner's view, *Dekker* is in the same field of endeavor and teaches pulsatile and non-pulsatile signal component extraction, with a concentration determined from the non-pulsatile component. The Examiner has taken the position that it would have been obvious to one of ordinary skill in the art at the time of the invention to obtain concentration, flow and volume measures from pulsatile and non-pulsatile signal components.

Moreover, in the Examiner's view, *Pfieffer et al.* as appended by *Dekker* includes all features of the invention as substantially claimed in claims 2, 5, 6, 10, 14, 15, 17, 18, 21 and 24, with the exception of the steps of using a threshold value, extrapolation of a scaled inflow function, and applying a locally increased contact pressure. In the Examiner's view, *Boas* is in the same field of endeavor and teaches establishing a threshold for dye concentration comparison, extrapolating the position from the scaled inflow function for determining the location of an ischemic event, and applying contact pressure. The Examiner has taken the position that it would have been obvious to one of ordinary skill in the art at the time of the invention to include the steps of using a threshold value for

comparison purposes and extrapolation of data for determining location as taught by *Boas* with the method according to *Pfieffer et al.*, in order to evaluate an ischemic event.

Pending dependent claim 19 does not appear to be addressed in the Examiner's July 9, 2008 Office Action and Applicants respectfully request clarification of the status of claim 19.

The rejections are respectfully traversed.

As set forth in amended independent claims 1 and 13, Applicant's invention provides a device and a method, respectively, for measuring blood flow in an organ using an injected indicator. As recited in amended claim 1, the device includes a radiation source for emitting near infrared radiation into tissue of the organ at a first location, a sensor for detecting a proportion of the emitted near infrared radiation that exits from the organ at a second location, and an evaluation unit that detects the proportion of the emitted near infrared radiation that exits from tissue of the organ as a <u>single</u> input signal. The evaluation unit is programmed to perform the following evaluation steps:

(a) dividing up the single input signal into a pulsatile component and a non-pulsatile component;

(b) determination of injected indicator concentration with reference to the organ tissue from the non-pulsatile component of the single input signal;

(c) iterative determination, from the non-pulsatile component, of an inflow function i(t) that characterizes blood flow through the organ by incrementally varying a mean transit time mtt until a stop criterion is reached;

(d) determination of injected indicator concentration with reference to blood volume in the organ from the pulsatile component of the single input signal and the iteratively determined inflow function i(t);

(e) calculation of blood volume in the organ as a quotient of the injected indicator concentration with reference to the organ tissue and the injected indicator concentration with reference to the blood volume in the organ; and

(f) calculation of the blood flow in the organ as a quotient of the blood volume in the organ and the mean transit time mtt when the stop criterion has been reached.

These steps (a)-(f) are also recited in amended method claim 13.

Amended independent claims 2 and 14 incorporate the subject matter of amended claims 1 and 13, respectively, and further recite scaling the inflow function i(t) by means of values determined from the pulsatile component of the single input signal.

Amended independent claim 24 incorporates the subject matter of claim 2 as amended and further recites the subject matter of cancelled claim 3, in particular back-extrapolation of the scaled inflow function i(t) to a time of injection of the indicator.

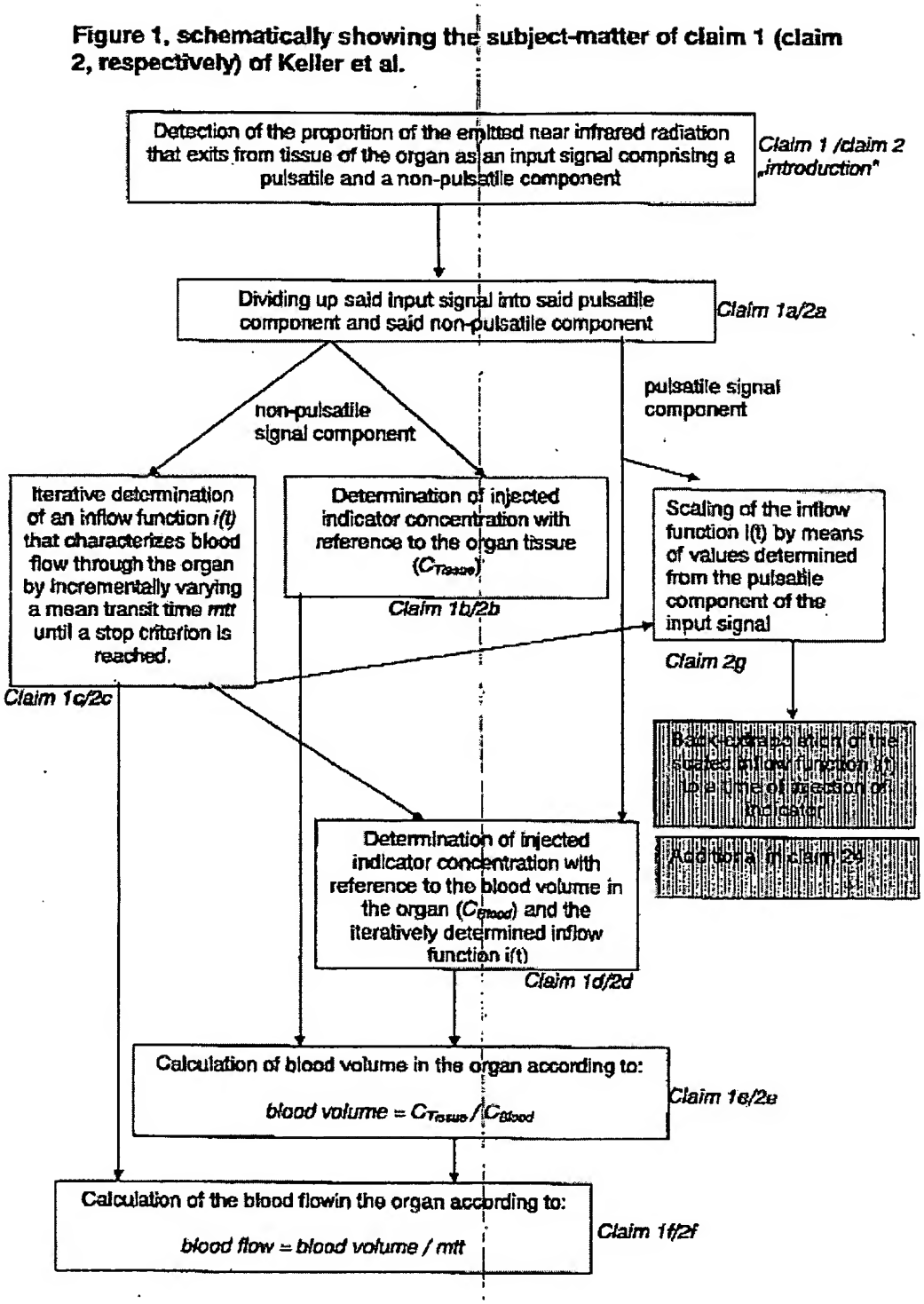
None of the cited references discloses or suggests the device and method as recited in the pending claims. The references also fail to achieve the substantial benefits that result from the device and method as recited in Applicants' claims. As set forth in detail below, the cited references considered alone or in combination fail to teach or suggest at least the following features of Applicant's claims:

- calculating blood flow and blood volume in an organ based on a single detected input signal (all claims);
- iteratively determining, from a non pulsatile component of the single measured input signal, an inflow function (i(t)) that characterizes blood flow through the organ by incrementally varying a mean transit time (mtt) unitl a stop criterion is met (all claims); and
- scaling the inflow function (i(t)) by means of values determined from a pulsatile component of the single measured input signal (claims 2, 14, 15 and 24).

In particular, the device and method as recited in amended claims 1, 2, 13, 14 and 24 relate to an evaluation technique based on a single detected input signal which is then divided up into a pulsatile component and a non-pulsatile component. Said pulsatile and non-pulsatile components are further used to determine blood flow and blood volume in an organ. This technique is in contrast to the calculations disclosed in *Pfeiffer et al.* (US 6,223,069), which require at least two separately measured input signals.

In order to highlight the differences between Applicant's amended claims and the process and method according to *Pfeiffer et al.*, the following two figures are provided. Figure 1 schematically illustrates the subject matter of Applicant's independent claims 1 and 2 and Figure 2 schematically illustrates the method disclosed in the cited *Pfeiffer et al.* reference.

Figure 1, schematically showing the subject-matter of claim 1 (claim 2, respectively) of Keller et al.



As recited in amended claims 1 and 2, Applicant's invention provides a device for measuring blood flow in an organ using an injected indicator. The claimed device includes a radiation source for emitting near infrared radiation into the tissue of the organ at a first location and a sensor for detecting a proportion of the emitted near infrared radiation that exits from the organ at a second location.

The claimed device further includes an evaluation unit. As shown schematically in Figure 1 above, the evaluation unit detects the proportion of the emitted near infrared radiation that exits from the tissue of the organ as a single input signal. The evaluation unit is programmed to perform the following steps, as shown. The single input signal is divided up into a pulsatile component and a non-pulsatile component (claim 1, paragraph (a); claim 2 paragraph (a)).

Subsequently, the non-pulsatile component of the single input signal is used to determine the injected indicator concentration with reference to the organ tissue (C_{tissue}) (claim 1, paragraph (b); claim 2, paragraph (b)). Furthermore, an inflow function (i(t)) is determined iteratively from the non-pulsatile component of the detected single input signal by

incrementally varying a mean transit time (mtt) until a stop criteria is met. This inflow function (i(t)) characterizes blood flow thought the organ (claim 1, paragraph (c); claim 2, paragraph (c)).

In a further step, the iteratively calculated inflow function (i(t)) and the pulsatile component of the detected single input signal are used for determining the injected indicator concentration with reference to blood volume in the organ (C_{blood}) (claim 1, paragraph (d); claim 2, paragraph (d). The blood volume in the organ is then calculated as a quotient of the determined C_{tissue} and C_{blood} (claim 1, paragraph (e); claim 2, paragraph (e)).

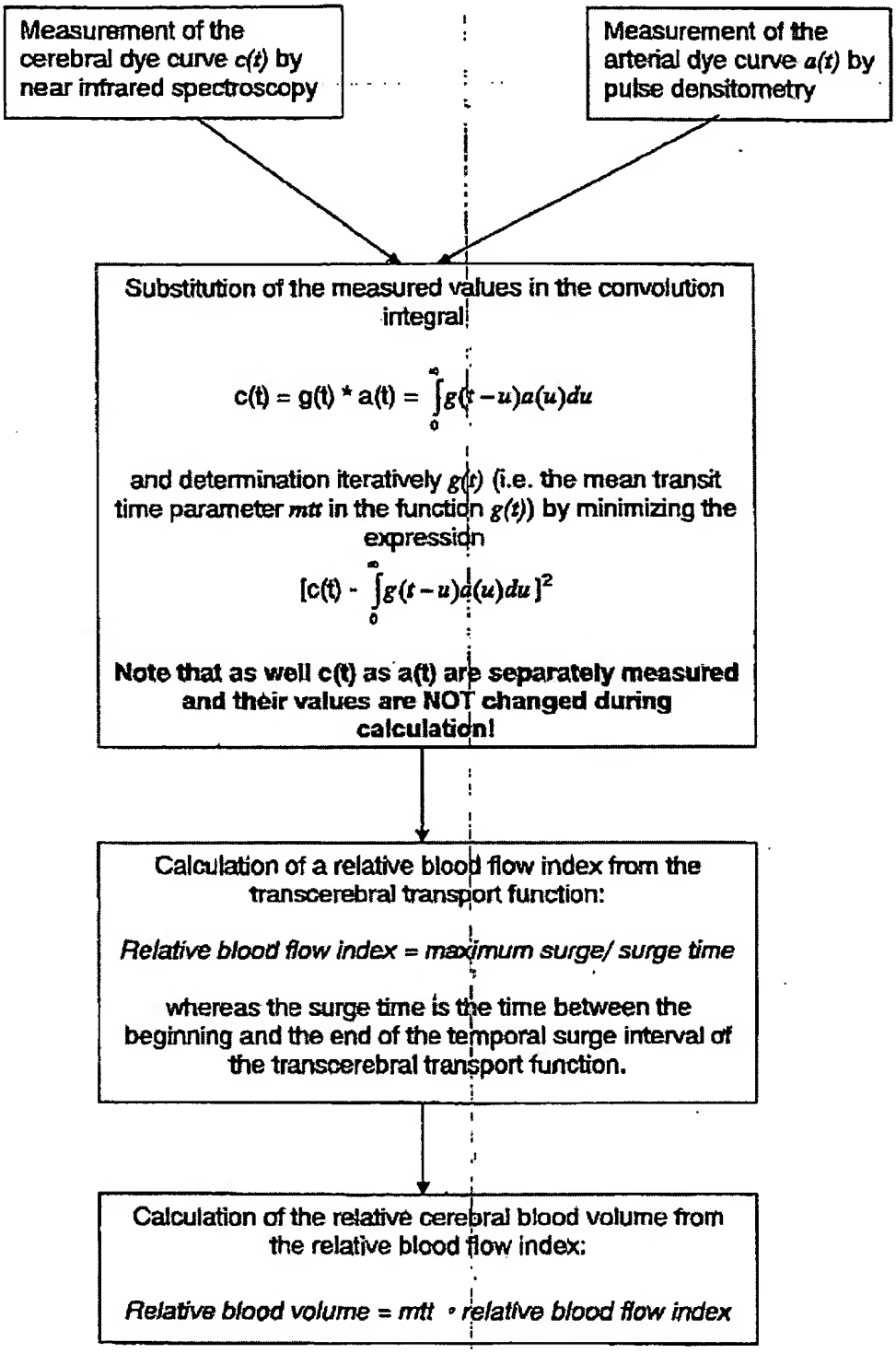
In the last step recited in amended claim 1 and also recited in amended claim 2, the blood flow in the organ is calculated as a quotient of the determined blood volume in the organ and mean transit time (mtt) (claim 1, paragraph (f); claim 2, paragraph (f)).

Additionally, as recited at paragraph (g) of claim 2 and shown in Figure 1 above, the calculated inflow function (i(t)) is

scaled by means of values determined from the pulsatile component of the single input signal.

In contrast to Figure 1, Figure 2 below schematically depicts the technique for measuring a cerebral blood volume and a cerebral blood flow index according to *Pfeiffer et al.*

Figure 2, schematically showing the evaluation process disclosed by Pfeiffer et al. (U.S. 6,223,069)



In contrast to the device and method recited in Applicant's amended claims, which require only a single input signal, as shown, *Pfeiffer et al.* teaches to measure separately at least two input signals, namely a cerebral dye curve (*c(t)*) and an arterial dye curve (*a(t)*). All calculations in *Pfeiffer et al.* are based on these two separately measured input signals. In order to perform the required calculation according to *Pfeiffer et al.* it is necessary to measure at least two separate input signals, whereas the calculations as recited in Applicant's pending claims can be performed by measuring only a single input signal. This feature of Applicant's claimed device and method constitutes a substantial advance and provides substantial benefit.

Pfeiffer et al. substitutes the two measured signals, *c(t)* and *a(t)* in the convolution integral:

[1]

$$c(t)=_{O}\int^{\infty} g(t-u)a(u)\,du,$$

(col. 5, line 10), wherein *g(t)* represents a transcerebral transport function. This equation [1] can be rewritten according to the mathematical definition of the convolution operator as

[2] $c(t) = g(t)* a(t)$

(*see e.g.* http://en.wikipedia.org/wiki/Convolution).

On page 4, line 4 of the July 9, 2008 Office Action, the Examiner has indicated that the auxiliary variable *u* provides a scaling factor, as recited in Applicant's claim 2, 14 and 24. This is incorrect, since as mentioned above, the convolution integral [2] is equivalent to the integral [1] and thus the variable *u* is an auxiliary variable of integration (as also described correctly in *Pfeiffer et al.* at column 5, line 11) and not a scaling factor as interpreted by the Examiner.

At column 5, lines 12-27, *Pfeiffer et al.* teaches the determination of the transcerebral transport function g(t) by an iterative, nonlinear matching process using iterative variation of the parameters of the transport function g(t). According to the principle of smallest squares, the squares of the differences between the measured cerebral concentrations and the result of the development of the measured arterial dye curve with the transport function (formula [3]) are minimized (col. 5, line 26)

[3] $$[c(t)-{}_{O}\int^{\infty} g(t-u)a(u)du]^2$$

Notably, in formula [3], the values of *c(t)* as well as the values of *a(u)* represent the separately measured signals of the cerebral dye curve and the arterial dye curve, respectively as described above. Thus the values of *c(t)* and *a(t)* are known and are neither changed nor scaled during the iterative calculation. Based on this explanation, it is clear that *Pfeiffer et al.* solely changes the parameters of the transport function in order to minimize iteratively the sum of the squares formula [3].

In contrast to the device and method recited in Applicant's claims, the method and device described in *Pfeiffer et al.* fail to adapt or recalculate the values of the inflow function *c(t)* or the outflow function *a(t)*. As recited in Applicant's amended claims 1 and 2, the values of the inflow function *i(t)* (which corresponds to the function *c(t)* in *Pfeiffer et al.*) are determined iteratively. In Applicant's claimed device and method, the inflow function *i(t)* is neither know *a priori* nor measured. Thus, the determination of the inflow function *i(t)* as recited in Applicant's claims is substantially different from the determination of *c(t)* in *Pfeiffer et al.*

Moreover, as recited in Applicant's dependent claims 4 and 16 and shown in FIG. 2 of Applicant's application, the values of the outflow function *o(t)* (which corresponds to the function *a(t)* in *Pfeiffer et al.*) as well as the parameters of the transport functions *g(t)* are adapted in every iteration step during the evaluation.

Although the same convolution integral [2] is used in Applicant's claims 4 and 16 and in *Pfeiffer et al.*, as recited in Applicant's claims, neither the inflow function *i(t)* nor the outflow function *o(t)* are measured directly, but rather both *i(t)* and *o(t)* are determined by calculations. In contrast, in the method according to *Pfeiffer et al.*, both the values of the function *c(t)* and the values of the function *a(u)* represent directly and separately measured input signals. Accordingly, the calculations of the inflow function and the outflow function as recited in Applicant's claims are substantially different from the method according to *Pfeiffer et al.*

In particular, in Applicant's claimed device and method, neither *i(t)* nor *o(t)* are known at the beginning of the iteration process. Consequently, the evaluation process according to

Applicant's claims relies solely on one measured input signal which is then divided up into pulsatile and non-pulsatile components. These components are used in the calculations as specified in Applicant's claims, whereas *Pfeiffer et al.* requires two separately measured signals, i.e. the arterial and the cerebral dye curve.

This distinguishing feature of Applicant's invention is expressly recited in each of the independent claims which expressly recite a single input signal. Moreover each of the steps in Applicant's claims which refer to this signal recite "*said single input signal*", making it clear that all calculations are based on this single detected input signal.

Another major difference between *Pfeiffer et al.* and Applicant's claims is that the device and process according to *Pfeiffer et al.* fails to calculate the injected indicator concentration with reference to the organ tissue C_{tissue} and the injected indicator concentration with reference to the blood volume C_{blood}. Consequently, the calculation of the blood flow index as described in *Pfeiffer et al.* (given by the quotient of a maximum surge and a surge time, both of which are not specified in Applicant's claims) is substantially different from the

calculation method recited in Applicant's claims.

In summary, *Pfeiffer et al.* fails to teach or suggest the following features of Applicant's independent claims 1 and 2:

- to perform calculations based on a single measured input signal which is then divided up into a pulsatile and a non pulsatile component (claim 1(a), claim 2(a));

- to determine injected indicator concentration with reference to the organ tissue from the non-pulsatile component of the single input signal (claim 1(b), claim 2(b));

- to determine iteratively an inflow function (i(t)) that characterized blood flow through the organ by incrementally varying a mean transit time mtt until a stop criterion is reached (claim 1(c), claim 2(c));

- to determine an injected indicator concentration with reference to blood volume in the organ from the pulsatile component of the single input signal and the iteratively determined inflow function (i(t)) (claim 1(d), claim 2(d));

- to calculate blood volume in the organ as a quotient of the injected indicator concentration with reference to the organ tissue and the injected indicator concentration with refernce to the blood volume in the organ (claim 1(e), claim 2(e)); and

- to calculate blood flow in the organ as a quotient of the blood volume in the organ and the mean transmit time mtt when the stop criterion has ben reached (claim 1(f), claim 2(f)).

The above comments apply to Applicant's independent method claims 13 and 14 and to independent claim 24 as well, as these claims also recite the features set forth above.

In addition, the feature of scaling the inflow function by means of values determined from the pulsatile component of the single input signal as recited in independent claims 2, 14 and 24 is not taught or suggested in any of the cited references. As discussed above, it is respectfully submitted that the Examiner incorrectly interpreted the convolution integral described in *Pfeiffer et al.* as providing a scaling factor.

The defects and deficiencies of the primary reference to *Pfeiffer et al.* are nowhere remedied by the secondary references to *Dekker* or *Boas*.

As recognized by the Examiner, *Pfeiffer et al.* fails to disclose the use of a non-pulsatile component of the measured signal in the determination of concentration and blood flow. Moreover, *Pfeiffer et al.* nowhere mentions or differentiates between a pulsatile and a non-pulsatile component of the two signals, c(t) and a(t) measured therein. The Examiner, however

has cited *Dekker* for the teaching of pulsatile and non-pulsatile signal component extraction with a concentration determined from the non-pulsatile (dc) component.

Applicant respectfully submits that one of ordinary skill in the art would not have modified the device or method according to *Pfeiffer et al.* in the manner proposed. In particular, it would not have been obvious to one of ordinary skill in the art to adapt the technique according to *Pfeiffer et al.* in view of *Dekker* in a way that the four signal components (i.e. the pulsatile and non-pulsatile components of *Pfeiffer et al.*'s measured arterial and cerebral dye curves) could be used or processed in a way to adapt or improve the described evaluation.

Boas also fails to teach or suggest at least the features of Applicant's claims as set forth in the above discussion of *Pfeiffer et al.*

For the reason set forth above, Applicant believes the claims, which are 1, 2 and 4-24, are allowable over the cited references, considered alone or in combination.

In summary, independent claims 1, 2, 13, 14 and 24 have been amended. In view of the foregoing, it is respectfully requested that the claims be allowed and that this application be passed to issue.

Respectfully submitted,
Emanuela KELLER

Edward J Callagh

COLLARD & ROE, P.C
1077 Northern Boulevard
Roslyn, New York 11576
(516) 365-9802

Frederick J Dorchak, Reg.No.29,298
Edward R. Freedman, Reg.No.26,048
Edward J Callaghan, Reg. No. 46,594
Attorneys for Applicants

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the U.S. Postal Service as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on October 3, 2008.

Amy Klein

Amy Klein

R:\Patents\K\KELLER E ET AL 1\Amendment in Response to 7 9 2008 Non Final OA .wpd